REMARKS

Rejection under §112, second paragraph

The claims have been amended as suggested, by adding the conventional and known definitions of amino acid symbols E, A, Y, and X.

Rejection under §112, first paragraph (Item Nos. 7 and 8 in Office action)

The specification discloses a complete sequence of a human aspartoacylase, as well as mutations in it. These full-length sequences inherently disclose fragments, and therefore provide a written description of the claimed invention. *Fiers v. Revel*, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993), cited on Page 4 of the Office action, is not relevant since that case involved an interference proceeding in which the losing party Fiers had not succeeded in isolating a single cDNA clone, but instead relied upon an allegedly enabled plan to isolate the DNA. The court rejected Fiers's arguments, requiring that an inventor actually have isolated the gene in order to have conceived of it for the purpose of establishing a date of invention. This application discloses the isolation and complete sequence of a number of different full-length sequences for human aspartoacylase, and therefore does not possess the defect alleged to be present in the Fiers specification.

In the present application, it is evident that the inventors conceived of, and had possession of, fragments of human aspartoacylase having the claimed properties. The specification provides a number of specific examples of polypeptide fragments, including, e.g., SEQ ID NOS: 10-16, and 24-27. Furthermore, the specification also describes amino acids motifs involved in enzyme catalysis, e.g., which can comprise a fragment that is capable of hydrolyzing N-acetyl aspartic acid to aspartate and acetate. See, Page 9, lines 1-14; Page 31, lines 22-29. Thus, it is clear that the inventors had possession of the claimed fragments on the application filing date.

The specification also provides adequate information and guidance to carry out the full scope of the claims. For example, assays are described for determining enzyme activity and immunological activity. See, e.g., Specification, Page 23, line 20-Page 24, line 9. Moreover, as mentioned above, amino acid motifs involved in the catalytic activity of esterases are identified in the specification See, Page 9, lines 1-14; Page 31, lines 22-29. Methods for determining whether a fragment possesses the recited activities are conventional, as well as being described in the specification. See, e.g., Page 17, lines 1-23; Page 23, line 29-Page 24, line 9. In conclusion, it is evident that the claims are fully described and enabled.

An analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. See, M.P.E.P. 2164.01. The standard for determining whether the specification meets the enablement requirement is whether is the experimentation needed to practice the invention undue or unreasonable. See, e.g., *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. See, M.P.E.P. 2164.01. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). See, M.P.E.P. 2164.01. The examiner has failed to meet her burden in establishing an enablement deficiency, and therefore the rejection should be withdrawn.

Rejection under §112, first paragraph

Claim 92 is rejected under 112, first paragraph as allegedly not enabled. See, Office action, Page 9. The specification provides at least three different examples of naturally-occurring mutant alleles, including mutations at amino acid positions 285, 231, and 305 of the wild-type

aspartoacylase polypeptide. Additional mutations can be isolated without undue experimentation. For instance, at least seven different methods are disclosed in the specification for identifying mutations in patient samples, including direct sequencing, heteroduplex analysis, restriction digestion analysis, single strand conformation polymorphism (SSCP), enzymatic activity, and immunoassay. See, e.g., Specification, Page 22, line 21-Page 24, line 9. Examples 7, 11, and 12 describe the isolation of three different mutant alleles using a combination of PCR, direct sequencing, SSCP, and restriction digestion analysis. This information, coupled with the skilled worker's knowledge is adequate to satisfy the statutory requirements of §112, first paragraph.

The specification also discloses conserved motifs that relate to enzyme activity, e.g., at amino acid positions 18-24, 275-278, and 293-289. See, e.g., Fig. 2; Specification, Page 8, line 33-Page 9, line 4; Sequence Disclosure Statement. Consistently, the mutation at position 285 is associated with a loss of enzyme activity. Additionally, the nonsense mutation at position 231 codes for a truncated form of the enzyme that lacks two of the three functional regions, and predictably, has no aspartoacylase activity. Thus, the specification describes several conserved regions that, when mutated, result in altered enzyme activity. Taken together, it is evident that the specification provides sufficient guidance to carry out the full scope of the claims.

Rejection under §102

It is stated in the Office action that Matalon et al., *J. Inher. Metab. Dis.*, 12 *Suppl.* 2, 329-331, 1989, "teach ... isolated and purified human aspartoacylase. This rejection is traversed on several grounds. For example, the Matalon et al. reference is not enabling. A patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research, 346 F.3d 1051, 1054 (Fed. Cir. 2003) On Page 331, lines 5-6, of Matalon et al., it was stated that "Aspartoacylase was purified to homogeneity from human and bovine brain" and cites this work

as unpublished data by co-inventors Kaul and Matalon. No information or guidance is provided on how such alleged purification was achieved. Similar non-enabling statements were made in other related publications, but strikingly no detailed procedure was ever disclosed. ("Furthermore, aspartoacylase from human brain and cultured skin fibroblasts ... follows a similar scheme of purification." See, Page 134 of Kaul et al, *J. Neurochem.*, 56:129-135, 1991; filed in the December 18, 2001 IDS and already considered by the examiner) ("We have now purified aspartoacylase to more than 1,100 fold enrichment from human and bovine brain ..."; from Kaul et al. 1988 abstract in the *American Journal of Human Genetics*; cited by the examiner in the §102(b) rejection in the Office action dated July 2, 2004, and subsequently overcome by applicants.) Thus, no specific protocol was provided that would enable the successful purification of a human aspartoacylase from a naturally-occurring source, e.g., where amounts are limiting.

Matalon et al. also does not describe a recombinant and purified human aspartoacylase (e.g., claim 67), or a human aspartoacylase produced in a host cell (e.g., claims 74, 75, 89, and 90). The limitations do impart patentable weight, contrary to the statements on Page 8 of the Office action. §2113 of the M.P.E.P. expressly states: "The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., In re Garnero, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)."

Furthermore, the Federal Circuit in *Fiers v. Revel*, 84 F.2d 1164; 1993 U.S. App. LEXIS 699; 25 U.S.P.Q.2D (BNA) 160, expressly held:

> Our statement in Amgen that conception may occur, inter alia, when one is able to define a chemical by its method of preparation requires that the DNA be claimed by its method of preparation. **We recognized that, in addition to being claimable by structure or**

> **physical properties, a chemical material can be claimed by means of a process**. A product-by-process claim normally is an after-the-fact definition, used after one has obtained a material by a particular process. Before reduction to practice, conception only of a process for making a substance, without a conception of a structural or equivalent definition of that substance, can at most constitute a conception of the substance claimed as a process. Conception of a substance claimed per se without reference to a process requires conception of its structure, name, formula, or definitive chemical or physical properties. (Emphasis added.)

Thus, the phrases at issue in the claims have been incorrectly ignored. When they are properly considered, it is evident that the claimed subject matter is distinguished over the cited prior art, e.g., because the claimed subject matter would be free of other proteins found in the naturally occurring source. Therefore, a **recombinant** human aspartoacylase produced in host cells as described and claimed in the application would possess distinctive characteristics, setting it apart from an aspartoacylase isolated by Matalon et al. The latter reference at most describes a preparation enriched in human aspartoacylase. Because it was isolated from its naturally-occurring source, this preparation would be contaminated with human proteins normally present with it. Claim 71 expressly states that claim aspartoacylase is "free of other human protein," a concept that was clearly possessed by the inventors, e.g., by virtue of recombinant production, and is therefore described in the specification as filed, albeit not in *ipsis verbis*. See, e.g., Specification, Page 15, lines 14-28; Page 17, lines 30-33. See, also WO 91/02796 which is cited therein for the disclosure of hosts cells and production of polypeptides free of other human proteins.

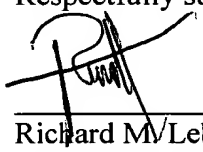
Additionally, Matalon et al. does not disclose human aspartoacylase which would be suitable as a pharmaceutical preparation. See, e.g., Claim 69. The preparation produced by Matalon et al. is obtained from a natural human tissue, and could be contaminated with

extraneous human proteins, viruses, bacteria, and other cellular components. For similar reasons, Claim 72 is also patentable over Matalon et al. since the latter would have contained extraneous components, and would not consist essentially of human aspartoacylase.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Attorney Docket No.: SHUTT-0001-C01

Date: January 26, 2006